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# Exploring synergy between azole antifungal drugs and statins for *Candida auris*

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**Background:** Global emergence of rapidly developing resistance to multiple antifungal drugs and high mortality pose challenges to the treatment of invasive *Candida auris* infections. New therapeutic approaches are needed, such as repurposing drugs including combination with antifungals. Statins have been reported to exert antifungal effects against various *Candida* species.

**Objectives:** Our study investigated potential synergy between the statins (rosuvastatin and fluvastatin) and azoles (voriconazole, posaconazole and isavuconazole) on clinical isolates of *C. auris*.

**Methods:** Twenty-one clinical isolates of *C. auris* were obtained. Chequerboard assays based on the CLSI broth microdilution method were used to assess synergy based on FIC index (FICI) calculations of MICs of individual drugs and in combinations.

**Results:** Single drug geometric mean (GM) MICs of fluvastatin and rosuvastatin were ≥128 mg/L in all 21 isolates. GM (range) MICs of posaconazole, voriconazole and isavuconazole were 0.259 (0.016–1 mg/L), 0.469 (0.016–2 mg/L) and 0.085 (0.004–1 mg/L), respectively. Combination of azoles with fluvastatin showed synergy in 70%–90% of *C. auris* isolates. In particular, voriconazole/fluvastatin resulted in 16-fold reduction in voriconazole MIC and synergy in 14/21 (67%) isolates. Posaconazole/fluvastatin resulted in 8-fold reduction in posaconazole MIC and synergy in 19/21 (90%) isolates.
Combining rosuvastatin with the azoles also showed synergy against *C. auris* in 40%–60% of the isolates and additive effect in 40%–50%. None of the combinations was antagonistic.

**Conclusions:** Our results provide a rationale for pursuing *in vivo* synergy tests as well as clinical studies to explore tolerability, treatment outcomes, optimal dose and exposure targets.

## Introduction

In the last 10 years, *Candida auris* has established it presence with outbreaks or invasive infections in multiple countries.[1] It can be divided into four major clades: South Asia, East Asia, Africa and South America, although a fifth clade has been described.[2]

Azoles are potent treatment options for *Candida* infections, with voriconazole, posaconazole and isavuconazole demonstrating $MIC_{90}$ of 0.125–2 mg/L against *C. auris*.[1,3,4] However, clinical isolates of *C. auris* show high MICs of fluconazole with 87%–100% resistance rates, in parallel with variable rates of resistance to other antifungal drugs.[1] Further, pandrug-resistant isolates, i.e. resistance to ≥2 classes of antifungal drugs including the echinocandins, have been increasingly observed with high mortality rates.[5,6]

Treatment guidelines for *C. auris* recommend echinocandins as first-line therapy in adult patients, and amphotericin B formulations in neonates and infants <2 months of age.[7] Both these drug classes must be given IV. Hence, if the activity of azoles

**Table 1.** Single drug MIC test against 21 clinical *C. auris* isolates

| Isolate no. | Origin (clade if known) | MIC (mg/L) | | | | |
|---|---|---|---|---|---|---|
| | | ISAV | POS | VRC | RSV | FLV |
| 1 | India | 0.016 | 0.0625 | 0.25 | 128 | 128 |
| 2 | India | 0.5 | 0.25 | 2 | >128 | >128 |
| 3 | India | 0.5 | 0.25 | 1 | >128 | >128 |
| 4 | South Africa | 0.0625 | 0.25 | 0.5 | 128 | 128 |
| 5 | South Africa | 0.25 | 0.5 | 2 | >128 | >128 |
| 6 | CDC | 0.016 | 0.016 | 0.016 | 128 | >128 |
| 7 | Perth, Australia | 1 | 1 | 2 | >128 | >128 |
| 8 | CDC (South American) | 0.0625 | 0.125 | 0.031 | 128 | 128 |
| 9 | CDC (South Asian) | 1 | 1 | 1 | >128 | >128 |
| 10 | CDC (South American) | 0.016 | 0.0625 | 0.016 | >128 | >128 |
| 11 | CDC (South Asian) | 1 | 1 | 2 | >128 | >128 |
| 12 | India | 0.016 | 0.25 | 0.25 | >128 | >128 |
| 13 | India | 0.016 | 0.125 | 0.125 | >128 | 128 |
| 14 | Perth, Australia | 0.125 | 0.5 | 1 | >128 | >128 |
| 15 | South Africa | 0.031 | 0.5 | 1 | >128 | >128 |
| 16 | RNSH Sydney, Australia | 0.125 | 0.5 | 2 | >128 | >128 |
| 17 | SEALS, Australia | 0.016 | 0.125 | 0.0625 | >128 | 128 |
| 18 | Fiona Stanley, Western Australia | 1 | 1 | 2 | >128 | >128 |
| 19 | India | 0.0625 | 0.5 | 0.5 | >128 | >128 |
| 20 | RNSH Sydney, Australia | 0.0625 | 0.25 | 2 | >128 | >128 |
| 21 | RNSH Sydney, Australia | 0.004 | 0.125 | 1 | >128 | 128 |
| GM MIC | | 0.085 | 0.259 | 0.469 | ≥128 | ≥128 |
| Range | | 0.004–1 | 0.016–1 | 0.016–2 | all isolates | all isolates |

ISAV, isavuconazole; POS, posaconazole; VRC, voriconazole; RSV, rosuvastatin; FLV, fluvastatin; RNSH, Royal North Shore Hospital; SEALS, South Eastern Area Laboratory Services.

could be increased by their combination with other oral agents with resultant synergy, this would offer early and effective 'step down' or even initial therapy options. One class of such agents is the statins, showing anti-inflammatory and direct growth-inhibitory effects on microorganisms.[8] Traditionally, combination of azoles with statins has been considered a risk due to drug–drug interactions. However, posaconazole and isavuconazole are less strong inhibitors of human CYP450 enzymes and some statins are less of a substrate of these enzymes.[9]

In our study, two statins (fluvastatin and rosuvastatin) were selected based on minimal drug–drug interaction risks[9] and previously reported synergy against other *Candida* species.[8]

These were investigated for potential synergy with azoles (voriconazole, posaconazole and isavuconazole) against *C. auris*.

## Materials

Twenty-one clinical isolates of *C. auris* obtained from the Clinical Mycology Reference Laboratory, Centre for Infectious Diseases and Laboratory Services, Institute of Clinical Pathology and Medical Research at Westmead Hospital (Table 1) were studied. They were from Australia ($n=7$), India ($n=6$), the US CDC ($n=5$) and South Africa ($n=3$). All isolates were cultured on Sabouraud dextrose agar for 24–48 h at 35°C and identity confirmed by internal transcribed spacer sequencing[10] and MALDI-TOF MS (Bruker Daltonics, Germany). Voriconazole, posaconazole and fluvastatin were purchased from Sigma–Aldrich, Australia, and isavuconazole and rosuvastatin from Sapphire Bioscience, Australia (all ≥98% purity).

## Methods

Drug susceptibility of 21 *C. auris* isolates was tested.[11] *Pichia kudriavzevii* (*Candida krusei*) ATCC 6258 was the quality control strain. Drug solutions were made by dissolving in DMSO then diluting in RPMI-1640 medium (with glutamine and phenol red but without bicarbonate) to allow for final well concentrations of 16–128 mg/L for fluvastatin and rosuvastatin, and 0.004–2 mg/L for voriconazole, posaconazole and isavuconazole.

For inoculum,[11] 0.5 McFarland suspensions of each *C. auris* isolate were prepared and diluted 1:50 then 1:20 in RPMI-1640 to a final inoculum of $1\times10^3$–$5\times10^3$ cfu/mL. A 96-well U-shaped plate was used for drug susceptibility testing and incubated at 35°C for 24 h. The MIC of the azole was the lowest concentration demonstrating 50% growth reduction relative to the control. MICs for each drug alone and azole/statin combinations were determined using the chequerboard broth microdilution method.[12] Each well was inoculated with the abovementioned *C. auris* and serial drug concentrations. The FIC index (FICI) was calculated using the equation: (MIC Drug A combined/MIC Drug A alone) + (MIC Drug B combined/MIC Drug B alone). FICI ≤ 0.5 was considered synergistic, 0.5 < FICI ≤ 1 additive, 1 < FICI < 4 no interaction and FICI ≥ 4 antagonistic. For statins, if there were still substantial growth at the

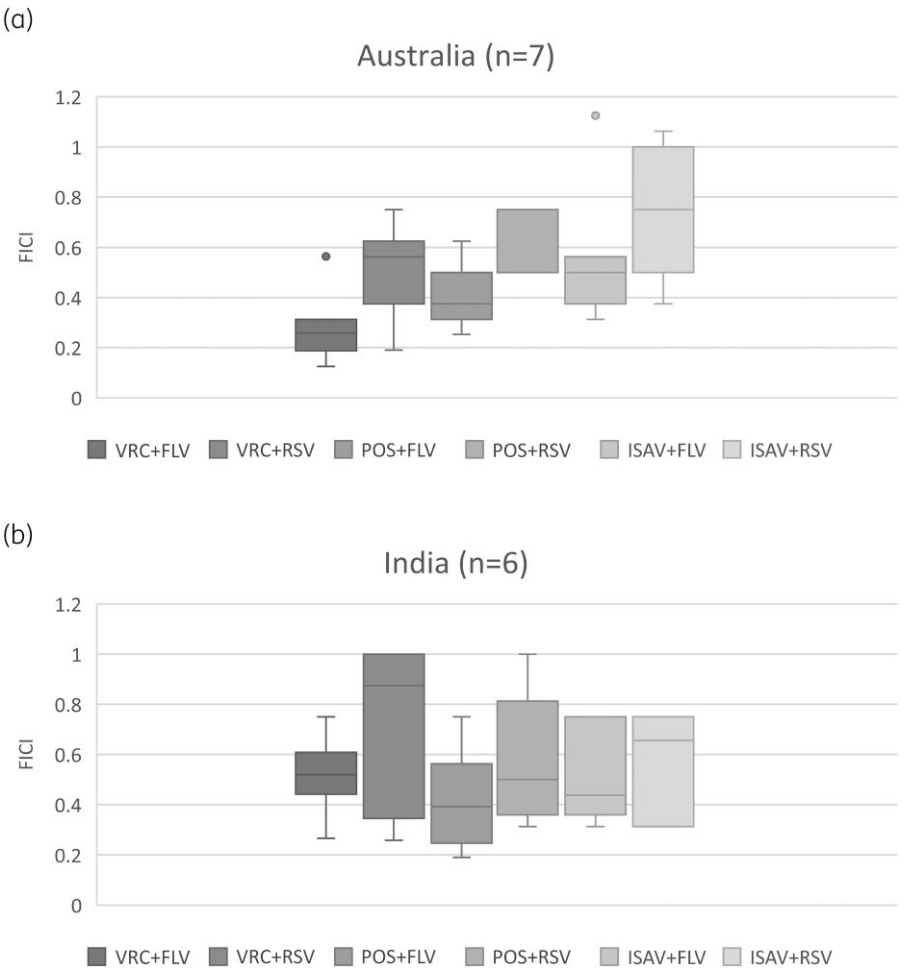


**Figure 1.** FICI for azole and statin combinations observed in isolates from (a) Australia and (b) India. Medians, first quartile and third quartile are represented by the middle, lower and upper lines of the box. Minimum and maximum values are represented by the lower and higher end of the whiskers. Individual dots represent the outliers. VRC, voriconazole; FLV, fluvastatin; RSV, rosuvastatin; POS, posaconazole; ISAV, isavuconazole.

maximum concentration tested (i.e. >128 mg/L), an MIC of 256 mg/L was assumed. Assays were performed in duplicate.

## Results

Fluvastatin and rosuvastatin alone showed MICs of ≥128 mg/L for the *P. kudriavzevii* ATCC 6258 and all 21 test isolates. Posaconazole, voriconazole and isavuconazole showed geometric mean (GM) MICs of 0.259 (range 0.016–1 mg/L), 0.469 (range 0.016–2 mg/L) and 0.085 (range 0.004–1 mg/L), respectively (Table 1). Currently no established interpretive clinical breakpoints (CBPs) or epidemiological cut-off values (ECVs) are available for azoles against *C. auris*,[13] except for the tentatively suggested BP of MIC ≥ 32 mg/L for fluconazole.[14] Based on the earlier data from our laboratory, fluconazole showed MICs of 128 mg/L, and hence no further synergy testing was performed (data on file, not shown).

In all combinations (Table 2), fluvastatin and rosuvastatin both showed at least 62%–74% reduction (from >128 to 33.1–49.1 mg/L) in their GM MIC values when combined with the azoles. This is based on the highest tested MIC of 128 mg/L for statins and potentially indicates even greater MIC reduction based on their true MIC values.

Voriconazole/fluvastatin showed a decreased GM MIC of 0.029/39 (range 0.004/16–1/128 mg/L) indicating 16-fold reduction in voriconazole MIC. The GM FICI was 0.288 (range 0.031–0.75), of which 14 of 21 isolates (67%) showed synergy and 7 (33%) showed additive effect.

Posaconazole/fluvastatin showed decreased GM MIC of 0.031/33.1 (range 0.004/16–0.25/128 mg/L), indicating 8-fold reduction in posaconazole MIC. The corresponding GM FICI was 0.341 (range 0.189–0.75). The majority of the isolates (19 of 21 isolates, 90%) showed synergy and 2 isolates showed additive effective.

Isavuconazole/fluvastatin showed decreased GM MIC of 0.022/33.1 (range 0.004/16–0.5/128 mg/L), indicating 4-fold reduction in isavuconazole MIC. Although the extent of MIC reduction was lower compared with other azoles, the GM FICI was 0.446 (range 0.189–1.13), with 15 (71%) isolates showing synergy. Five isolates (24%) showed an additive effect and one showed indifference.

**Table 2.** Combined drug MIC test and FICI against 21 clinical *C. auris* isolates

| Isolate no. | MIC ISAV/RSV | FICI ISAV/RSV | MIC ISAV/FLV | FICI ISAV/FLV | MIC POS/RSV | FICI POS/RSV | MIC POS/FLV | FICI POS/FLV | MIC VRC/RSV | FICI VRC/RSV | MIC VRC/FLV | FICI VRC/FLV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.008/64 | 0.75 | 0.004/64 | 0.75 | 0.0312/64 | 1 | 0.016/64 | **0.5** | 0.0625/16 | **0.375** | 0.06/64 | **0.5** |
| 2 | 0.125/128 | 0.75 | 0.125/128 | 0.75 | 0.0625/128 | 0.75 | 0.0625/128 | 0.75 | 0.03/32 | 1 | 0.25/128 | 0.75 |
| 3 | 0.25/16 | 0.563 | 0.125/32 | **0.375** | 0.0625/64 | **0.5** | 0.0625/64 | **0.5** | 0.008/64 | **0.258** | 0.5/16 | 0.56 |
| 4 | 0.004/64 | 0.564 | 0.008/64 | 0.628 | 0.0625/64 | **0.5** | 0.004/64 | **0.266** | 0.008/16 | **0.079** | 0.016/16 | **0.094** |
| 5 | 0.125/64 | 0.75 | 0.0312/64 | **0.375** | 0.125/64 | **0.5** | 0.008/64 | **0.266** | 0.008/64 | **0.254** | Jan-64 | 0.75 |
| 6 | 0.004/16 | **0.375** | 0.004/16 | **0.313** | 0.004/16 | **0.375** | 0.004/16 | **0.313** | 0.004/32 | **0.375** | 0.008/16 | 0.56 |
| 7 | 0.25/64 | **0.5** | 0.5/16 | 0.563 | 0.25/64 | **0.5** | 0.125/64 | **0.375** | 0.125/16 | **0.19** | 0.016/32 | **0.258** |
| 8 | 0.008/64 | 0.57 | 0.004/16 | **0.189** | 0.0312/64 | 0.75 | 0.004/32 | **0.282** | 0.004/16 | **0.19** | 0.008/16 | **0.32** |
| 9 | 0.25/64 | **0.5** | 0.25/64 | **0.5** | 0.5/16 | 0.563 | 0.125/64 | **0.375** | 0.125/32 | **0.25** | 0.125/16 | **0.188** |
| 10 | 0.004/16 | **0.313** | 0.004/16 | **0.313** | 0.004/16 | **0.189** | 0.004/16 | **0.189** | 0.004/16 | **0.031** | 0.004/16 | **0.031** |
| 11 | 0.5/64 | 0.75 | 0.5/64 | 0.75 | 0.5/32 | 0.625 | 0.25/32 | **0.375** | 0.5/64 | **0.375** | 0.25/64 | **0.375** |
| 12 | 0.004/16 | **0.313** | 0.004/16 | **0.313** | 0.0625/64 | **0.5** | 0.004/64 | **0.266** | 0.125/128 | 1 | 0.004/64 | **0.266** |
| 13 | 0.004/16 | **0.313** | 0.004/16 | **0.375** | 0.0312/32 | **0.375** | 0.004/32 | **0.282** | 0.0625/64 | 1 | 0.004/64 | 0.532 |
| 14 | 0.0625/128 | 1 | 0.0312/64 | **0.5** | 0.125/64 | 0.75 | 0.125/16 | **0.313** | 0.5/64 | 0.75 | 0.008/64 | **0.258** |
| 15 | 0.008/64 | **0.5** | 0.0058/16 | **0.313** | 0.125/16 | **0.313** | 0.125/16 | **0.313** | 0.004/128 | 0.504 | 0.0312/32 | **0.156** |
| 16 | 0.0312/32 | 0.375 | 0.0312/16 | 0.313 | 0.25/16 | 0.625 | 0.125/16 | **0.375** | 0.125/128 | 0.563 | 0.125/64 | **0.313** |
| 17 | 0.004/64 | 0.5 | 0.004/32 | 0.5 | 0.0625/32 | 0.75 | 0.0625/16 | 0.625 | 0.004/64 | 0.564 | 0.004/64 | 0.564 |
| 18 | 0.25/128 | 0.75 | 0.125/64 | 0.375 | 0.25/128 | 0.75 | 0.25/16 | **0.313** | 0.25/64 | **0.375** | 0.125/32 | **0.188** |
| 19 | 0.016/128 | 0.75 | 0.016/64 | 0.5 | 0.125/16 | **0.313** | 0.0625/16 | **0.19** | 0.125/128 | 0.75 | 0.004/128 | 0.508 |
| 20 | 0.0625/16 | 1.063 | 0.0625/32 | 1.125 | 0.125/64 | 0.75 | 0.0625/64 | **0.5** | 0.25/64 | **0.375** | 0.004/64 | **0.254** |
| 21 | 0.004/128 | 0.75 | 0.004/16 | 0.378 | 0.0312/64 | **0.5** | 0.016/16 | **0.253** | 0.125/128 | 0.625 | 0.0625/16 | **0.125** |
| GM | 0.026/49.1 | 0.568 | 0.022/33.1 | 0.446 | 0.074/41.7 | 0.529 | 0.031/33.1 | 0.341 | 0.040/49.1 | 0.364 | 0.029/39 | 0.288 |
| Range | 0.004/16–0.5/128 | 0.313–1.06 | 0.004/16–0.5/128 | 0.189–1.13 | 0.004/16–0.5/128 | 0.189–1 | 0.004/16–0.25/128 | 0.189–0.75 | 0.004/16–0.5/128 | 0.031–1 | 0.004/16–1/128 | 0.031–0.75 |

ISAV, isavuconazole; POS, posaconazole; VRC, voriconazole; RSV, rosuvastatin; FLV, fluvastatin. MIC expressed in mg/L. Bold FICI values represent synergy (≤0.5).

Combination of rosuvastatin with voriconazole resulted in a slightly lower proportion of isolates demonstrating synergy (12 of 21 isolates, 57%) and 9 (43%) showed additive effect. The GM FICI was 0.364 (range 0.031–1). This combination resulted in a pronounced decrease in voriconazole MIC, similar to voriconazole/fluvastatin, and demonstrated about 12-fold reduction with GM MIC of 0.040/49.1 (range 0.004/16–0.5/128 mg/L).

Isavuconazole/rosuvastatin showed only 3-fold reduction in isavuconazole MIC with decreased GM MIC of 0.026/49.1 (range 0.004/16–0.5/128 mg/L). The GM FICI was 0.568 (0.313–1.06), of which 9 (43%) isolates showed synergy, 11 (52%) showed additive effect and 1 showed no difference.

Comparably, posaconazole/rosuvastatin showed 4-fold reduction in posaconazole MIC with decreased GM MIC of 0.074/41.7 (range 0.004/16–0.5/128 mg/L). The GM FICI was 0.529 (0.189–1), of which 11 (52%) of 21 isolates showed synergy and 10 (48%) showed additive effect. None of the drug combinations tested resulted in antagonism.

Regional differences in FICI were not obvious due to the small number of isolates (mostly ≤3 isolates) not allowing distribution analysis. However, seven isolates from Australia and six from India still allowed preliminary assessment of FICI values in different azole and statin combinations (Figure 1). The variability in FICI values was more pronounced in isolates from India. We observed a trend of lower FICI for voriconazole/fluvastatin combination in isolates from Australia compared with isolates from India (median FICI 0.26 versus 0.52). Similarly, for voriconazole/rosuvastatin, FICI values showed a tendency of lower median values in isolates from Australia compared with India (median FICI 0.56 versus 0.88).

## Discussion

In our study, combining fluvastatin with posaconazole, voriconazole or isavuconazole resulted in synergistic effect in 70%–90% of the clinical *C. auris* isolates. In particular, voriconazole/fluvastatin showed 16-fold reduction in MIC of voriconazole alone, and posaconazole/fluvastatin showed 8-fold reduction in MIC of posaconazole alone. Although less pronounced, combining rosuvastatin with the azoles also showed synergistic effect against *C. auris* in 40%–60% of the isolates and additive effect in 40%–50% of the isolates.

Statins have been reported to have antifungal effects on various fungal pathogens including *Candida* spp., *Saccharomyces cerevisiae*, *Aspergillus* spp., mucormycetes and dermatophytes,[15] and to sensitize response to azoles and polyenes.[15,16]

A multicentre cohort study of 326 candidaemia patients also reported a significantly lower early 5 day case fatality rate of 4.5% in statin users, compared with 17% in non-statin users.[17]

Synergistic interactions between statins and azoles were explored for clinically important fungi including *Candida albicans* and *Candida glabrata*.[8] Itraconazole and rosuvastatin combination demonstrated synergy against 11 clinical isolates of *C. albicans* with interaction ratio (IR) of 1.79, and fluconazole and fluvastatin combination showed an IR of 1.70 (where IR > 0.5 indicates synergy). That study also observed no antagonistic effect from the azole and statin combination, as was the case in our study.

Potential synergy mechanisms could include statins' interruption of intracellular ergosterol biosynthesis through inhibition of HMG-CoA reductase, decreased activation of key cellular proteins involved in cellular respiration and metabolism, and apoptosis induction.[15] Azoles are also believed to interrupt ergosterol biosynthesis by inhibiting the cytochrome P450-dependent 14α-lanosterol demethylase.[8]

In a more recent study, a third-generation statin, pitavastatin, demonstrated synergy with voriconazole against 16 strains of *C. albicans*, *C. glabrata* and *C. auris* (ΣFICI ranged from 0.15 to 0.50, where ΣFICI ≤ 0.5 indicates synergy).[18]

Pitavastatin does not undergo major metabolism through cytochrome P450 (CYP), especially CYP3A4, just like rosuvastatin and fluvastatin, which undergo minimal metabolism by CYP2C9, thus reducing the potential for drug–drug interactions concerning azole and statin.[19]

Limitations of our study include potentially underestimated synergistic or additive interactions as the assumption was made for statin MICs of 256 mg/L for FICI calculations, when the growth still occurred at >128 mg/L. This also could mean that some of the weaker additive interactions with rosuvastatin could possibly be reclassified as synergistic to the greater extent if different maximum concentration was tested. However, the concentration ranges in our study are sufficient to define drug class-specific resistance and align with MIC testing in other studies.[20] The pronounced synergistic interactions between the azoles and statins for *C. auris* is notable. Larger sample size in each region would also have enabled statistical analyses to see regional differences in FICI values.

Overall, our study provides promising *in vitro* data for statin/azole combinations against *C. auris* and a good rationale for further exploration in murine models of disseminated *C. auris* infection, especially testing at clinically relevant drug concentrations.[21] As clinical data are now available to support prolonged combined use, a prospective multidose Phase 1 study demonstrating safety and tolerability in healthy volunteers is the essential next step. Surveillance data will enable better understanding of MIC distributions in different regions, and guide establishment of BP concentrations for azoles against *C. auris*. This will help define the role of statins in potentially reversing azole resistance in *C. auris* treatment.

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## Transparency declarations

All authors declare no conflict of interest.

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